Seizure 1998; **7**: 167–171

CASE REPORT

Hypothalamic hamartomas causing gelastic epilepsy: Two cases and a review of the literature

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Two cases of hypothalamic hamartomas causing gelastic epilepsy are described. The clinical presentations and the radiological features are presented, and the mechanisms involved in laughing attacks are discussed. The literature is reviewed and it is suggested the complete extirpation of the hamartomas is the treatment of choice in gelastic epilepsy.

Key words: hypothalamic hamartomas; gelastic epilepsy.

INTRODUCTION

Gelastic epilepsy, or laughter attacks (Greek gelos = laugh), may occur in association with hypothalamic hamartomas. The management of affected patients is difficult and controversial. In this report we present two patients to illustrate dilemmas in management, and have reviewed the literature associated with this condition.

CASE 1

This patient, an 8-year-old boy, presented to the paediatric neurology department after his teacher and classmates had reported to his parents that he had recently developed a tendency to prolonged spells of inappropriate giggling. This was followed by several minutes where he had a glazed expression and appeared distant. There were no obvious precipitating factors.

Examination showed him to be tall for his age but of normal intelligence and with no neurological features. An EEG showed an ill-defined right-sided abnormality and a CT scan was reported as normal.

He was started on carbamazepine but showed little improvement. One month later, he was admitted following a generalized seizure and vigabritin 500 mg bd was added.

Unfortunately his fits continued to increase until he was having between 10 and 20 seizures per day. These were sometimes spontaneous but oftenprecipitated by laughing and consisted of a short period of laughter followed by hand-clapping and various automatisms. On one occasion he put his shoes into the washing machine. He had loss of awareness of his surroundings and amnesia for the event.

A magnetic resonance imager (MRI) scan showed on T1-weighted images an isodense nonenhancing pedunculated mass within the interpenduncular cistern measuring 2.5 cm in diameter, with apparent compression of the hypothalamus. T2-weighted images revealed increased signal intensity. This was thought to be a hamartoma of the tuber cinereum. In view of the failure of his seizures to respond to medication, it was decided to admit him for assessment and surgery.

By the time of his admission he was still tall for his age (10 years) at the 98th centile and had evidence of development of secondary sexual characteristics.

At craniotomy a firm mass was found and was approached between the optic nerve and the carotid artery on the right. Unfortunately it was only possible

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to remove a portion of the mass. Histology showed mature brain tissue composed of neuropil, neurons or variable morphology, nests of small and differentiated cells, and aggregates of neurones resembling basal forebrain, islands of Caleja and myelinated tracts.

Postoperatively his fits were unchanged. He developed diabetes insipidus but responded well to Desamino-D-arginine-Vasopressin (DDAVP) treatment.

CASE 2

This 38-year-old lady had had epilepsy since the age of 2. She had a normal birth history and no febrile convulsions. Her seizures had always been badly controlled, but 3 years before admission deteriorated to a level where she was having five or six major seizures a month with frequent minor seizures. By the time of her admission to hospital she had been on carbamazepine and valproate up to the maximum tolerated dose. Vigabatrin, after an initial response, has resulted in worsening of seizures; lamotrigine and gabapentin had been poorly tolerated. While on the wards he had several seizures and these were observed to be preceded by attacks of uncontrollable laughter. This feature had not been mentioned by her or her husband at previous interviews.

An electroencephalogram (EEG) showed occasional runs of right temporal slow-wave activity but no definite focus. A MRI scan showed some generalized atrophy, particularly of the posterior fossa structures, and a well-defined right-sided mass in the region of the tuber cinereum.

At surgery via a pterional craniotomy the lesion was approached anterior and posterior to the carotid artery. A subtotal excision was made. Histology showed dense gliosis with an abnormal pattern of oligodendroglial cells and neurons. It was felt to be consistent with a hypothalamic hamartoma.

Postoperatively the patient remained seizure-free at 1-year follow up.

DISCUSSION

Laughter, the somatic expression of mirth, involves movements of facial muscles and is associated with clonic contractions of the thoracic cage and abdominal wall. Neurologically, this involves the limbic system, especially the anterior cingulate gyrus, and the brain stem[1]. Mirth, the emotional accompaniment of laughter, involved the basal temporal cortex, particularly the fusiform and parahippocampal gyri. The two systems interrelate with each other and with other cortical and subcortical regions, to produce a behaviour pattern which is thought to be unique to humans[1].

Pathological laughter is inappropriate, uncontrollable, often prolonged, and cannot be inhibited voluntarily. It can be elicited by trivial, non-specific stimuli. This has been observed in pseudobulbar and bulbar syndromes with a vascular, inflammatory, toxic or degenerative aetiology. It is probably due to a disorder of motor expression of emotion rather than of emotion itself. There is no associated EEG abnormality. This is distinct from the laughter of gelastic epilepsy where the duration of laughter is usually short (less than 30 seconds), although when associated with a complex partial seizure it may be more prolonged.

For a seizure to be considered gelastic, laughter has to be inappropriate, stereotyped, and not precipitated by either specific (joke–humour) or non-specific stimulus.

Gaskon and Lomboso (2) proposed the following criteria for the diagnosis of gelastic epilepsy:

1 stereotyped recurrence;

2 absence of external precipitants;

3 EEG abnormality, ictal or interictal;

4 absence of other causes of pathological laughter;

5 concomitant fits of other types are frequent.

Gelastic seizures can be isolated, or may be part of a complex partial seizure with loss of memory, automatism, and motor symptoms as in the two cases reported here. They are frequently associated with hypothalamic masses which are usually hamartomas: more than 45 cases with gelastic epilepsy[3] have been reported in the literature up to 1988.

Of 50 histologically verified cases from another report, 74% were associated with precocious puberty and 48% with gelastic seizures, generalized seizure and behavioural disturbances.

Ictal laughter may be rarely a component of complex partial seizures of temporal or frontal origin, or infantile spasms.

Most patients with gelastic seizures associated with hamartomas have an early onset of seizure activity and a variety of behavioural or psychiatric disorders. Most have a progressive reduction of intellectual functions.

Hypothalamic hamartomas

These are well-defined masses of mature ganglionic tissue which are usually attached to the tuber cinereum or the mamilliary bodies[5].

They may be sessile to pedunculated, usually extending into the interpeduncular cistern but sometimes into the floor of the third ventricle.

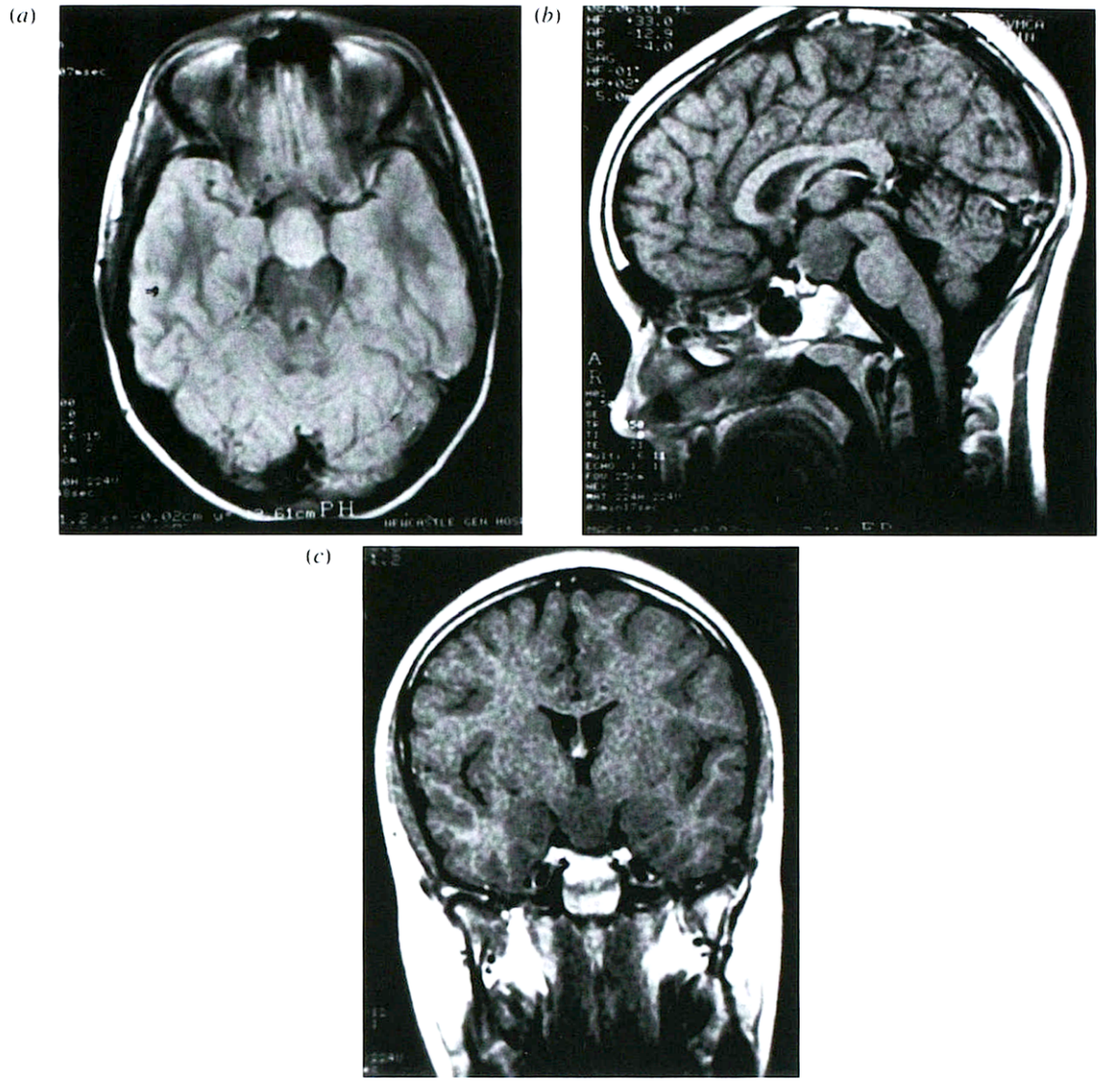

Fig. 1: a–c. Axial, sagittal and coronal MRI studies of Case 1 showing large midline hypothalamic mass.

Valdueza *et al*[6] have shown that the pendunculated hamartomas are more commonly associated with precocious puberty, whereas the sessile hamartomas are more commonly associated with gelastic seizures.

This is in accordance with clinical and radiological findings regarding our patients.

They consist of grey and white matter of varying degrees of differentiation, and indeed in some cases nerve fibres have been traced from the hamartoma into the tuberal region of the hypothalamus. They are often associated with cerebral or extracerebral congenital abnormalities, including microgyria, heterotopia, cysts, callosal defects, polydactyly, facial anomalies and heart defects[7–10].

The investigation of choice is MRI. On T1 images hamartomas appear as nonenhancing, isointense lesions, and on T2 they are either intense or slightly hyperintense[11]. They are unlikely for this reason to be confused with other lesions in the same area, such as craniopharyngioma, low-grade hypothalamic astrocytoma, ganglioglioma, optic pathway glioma, lymphoma, or suprasellar germinoma[12].

The presence of active neural tracts connecting a hamartoma and number of hypothalamic nuclei and providing a potential excitatory pathway may explain the presence of precocious puberty in many of these patients.

The pathogenesis of precocious puberty is not clear. It has been speculated that local pressure, abnormal neural connects, endocrine activity or a combination of these may play a part. Gullet *et al*[12] reported a patient with hypothalamic hamartoma and precocious puberty who showed normal pituitary function apart from a mature pattern of gonatrophin response to gonodotrophin releasing hormone (GnRH) together with elevated basal and stimulated prolactin concen-

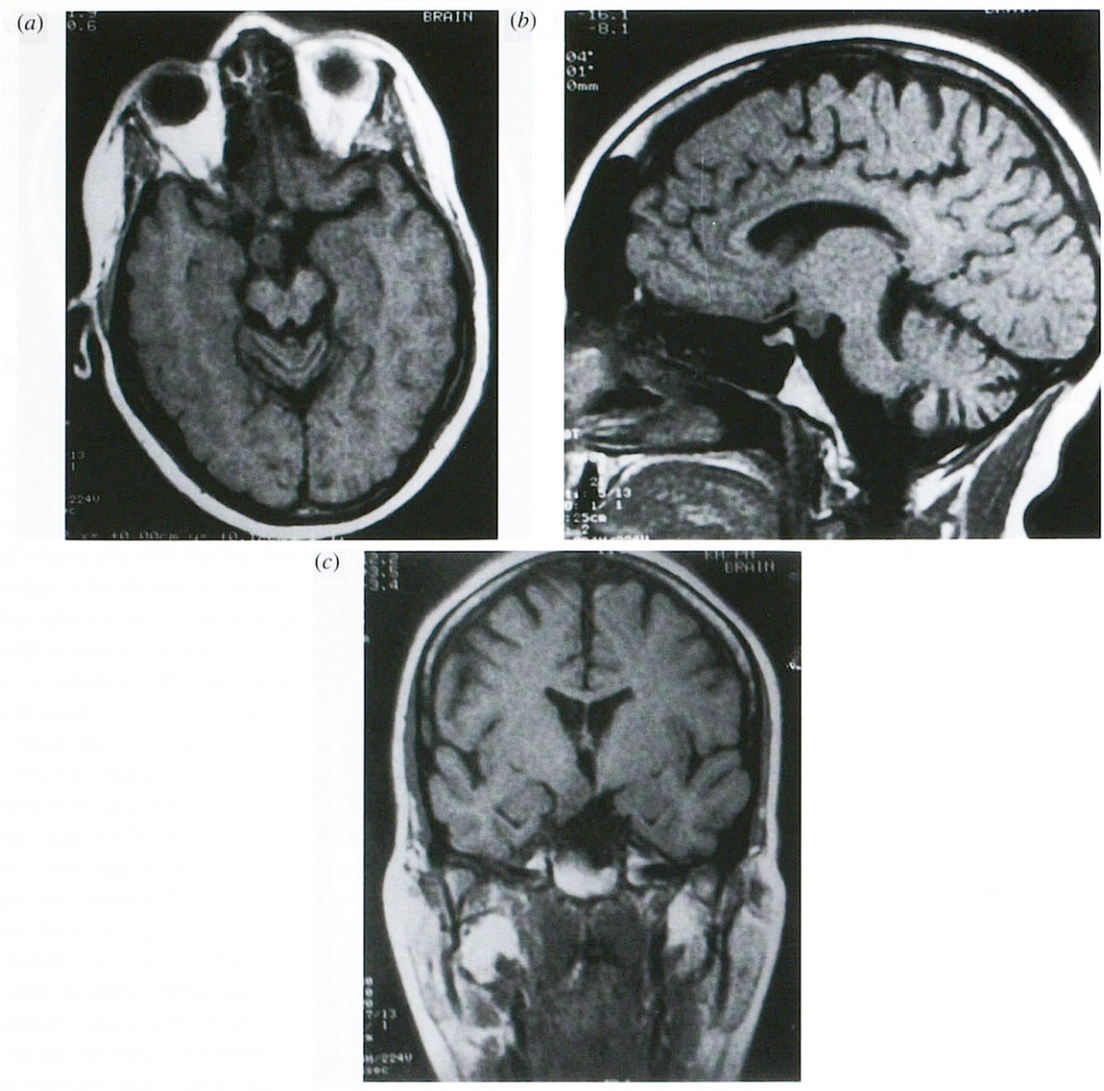

Fig. 2: a–c. Axial, sagittal and coronal MRI studies of Case 2 showing a unilateral hypothalamic mass.

trations. Tumour biopsy showed specific staining of neurons for GnRH. The occurrence of these tumours with precocious puberty in uncommon; only 22 cases have been reported since 1930. Despite the fact that our first patient had precocious puberty, immunoreactivity for GnRH was not observed, suggesting that the factors above could play a role. However, in mammals an intermittent pulsatile GnRH secretion is required for the induction of puberty, and it would be difficult to ascribe such a function to a hamartoma. It may therefore be that the normal pattern of pituitary responsiveness to GnRH stimulation is altered in such patients, or that the effect is produced by another mechanism such as local pressure.

Hypothalamic hamartomas have also been associated with diabetes insipidus, obesity and growth hormone secreting pituitary adenoma[13].

Treatment

Small hamartomas do not cause hypothalamic compression and may be asymptomatic, being found incidentally when the patient is scanned for another reason. They may cause precocious puberty, for reasons already discussed, but epilepsy is unusual. Treatment is therefore unlikely to be warranted. Precocious puberty, when present, should be treated to prevent ultimate short stature and control sexual development. Lutein-hormone-releasing hormone (LHRH) analogues decrease gonadotrophin levels and may be used for this purpose[12]. Hamartomas larger than 1.5 cm usually cause distortion of the mamillary bodies and the floor of the third ventricle. Patients usually have gelastic or other forms of epilepsy, and frequently exhibit psychological and behavioural problems which may be progressive. Progression does not seem to be due solely to the effects of epilepsy,

but rather to generalized degeneration of the limbic system. It is in these patients that surgical treatment may be considered. Epilepsy in such patient often proves difficult to control with drug treatment alone[3] and surgery may become necessary. So far 14 patients have been reported as being seizure free postoperatively after a total or subtotal resection had been achieved[6]. The principal surgical approach reported is frontotemporal or pterional craniotomy. The former is more useful when a portion of the lesion is in the third ventricle. Via the pterional approach, as in both our cases, the tumour is approached between optic nerve, carotid artery, and third nerve.

Many of these patients have temporal foci, and so some surgical approaches have been directed at resecting apparently epileptogenic cortex. A series of 12 patients with intractable gelastic epilepsy were reported in a study from Montreal[3]. Intracranial EEG recordings indicated an apparent focus in the temporal or frontal lobe, and eight of them underwent focal corticectome, six had interior temporal resection, one had a frontal lobectomy, and one had frontal lobectomy with corpus collosotomy.

No patients had a significant reduction in seizure frequency. This suggests that the apparent cortical abnormality is not the true focus.

It would seem, therefore, that surgery should be considered for lesions which, on sophisticated imaging studies, would appear to be surgically resectable. These would include pedunculated or unilateral lesions of moderate size, such as our second case. With careful surgery morbidity should be low and at least 30% likelihood of improvement in seizures would be expected. There would seem to be no place for extralesional resections[14].

Until recently, reports of surgical treatment showed little effect on seizures or cognitive decline[15], but a review of recent literature has shown good or excellent results in many cases[6]. Overall, surgery has a beneficial effect on seizures in about 30% of patients with a risk of amnestic disorders due to mamillary-body disturbance and of hypothalamic or pituitary upset.

CONCLUSIONS

Hamartomas of the hypothalamus may present people with precocious puberty, seizure disorders, particularly gelastic epilepsy, and progressive cognitive decline. While hormonal abnormalities are nowadays readily treatable, medical treatment for the epileptic disorders is difficult. In refractory cases, surgery should be considered in patients with a resectable lesion.

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